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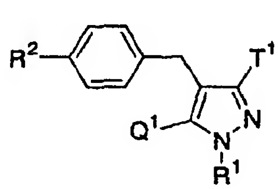
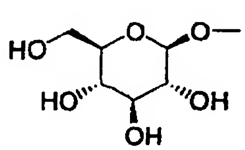
(54) GLUCOPYRANOSYLOXYPYRAZOLE DERIVATIVES, MEDICINAL COMPOSITIONS CONTAINING THE SAME AND INTERMEDIATES IN THE PRODUCTION THEREOF

(57) The present invention relates to glucopyranosyloxypyrazole derivatives represented by the general formula:



(I)

wherein R^1 represents a hydrogen atom or a lower alkyl group; one of Q^1 and T^1 represents a group represented by the general formula:



while the other represents a lower alkyl group or a halo (lower alkyl) group; and R^2 represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom, or pharmaceutically acceptable salts thereof, which have an inhibitory activity on human SGLT2 and are useful as agents for the prevention or treatment of diabetes, diabetic complications or obesity, and to pharmaceutical compositions comprising the same and intermediates thereof.

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Description

Technical Field

[0001] The present invention relates to glucopyranosyloxypyrazole derivatives or pharmaceutically acceptable salts thereof, which are useful as medicaments, pharmaceutical compositions comprising the same and intermediates thereof.

Background Art

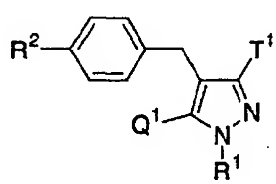
[0002] Diabetes is a lifestyle-related disease with the background of change of eating habit and lack of exercise. Hence, diet and exercise therapies are performed on patients with diabetes. Furthermore, when sufficient control and continuous performance are difficult, drug treatment is simultaneously performed. Biguanides, sulfonylureas and insulin sensitivity enhancers have been employed as antidiabetic agents. However, biguanides and sulfonylureas show occasionally adverse effects such as lactic acidosis and hypoglysemia, respectively. When using insulin sensitivity enhancers, adverse effects such as edema occasionally are observed, and it is also concerned in advancing obesity. Therefore, in order to solve these problems, it has been desired to develop antidiabetic agents having a new mechanism.

[0003] In recent years, development of new type antidiabetic agents has been progressing, which promote urinary glucose excretion and lower blood glucose level by preventing excess glucose reabsorption at the kidney (J. Clin. Invest., Vol.79, pp.1510-1515 (1987)). In addition, it is reported that SGLT2 (Na^+/glucose cotransporter 2) is present in the S1 segment of the kidney's proximal tubule and participates mainly in reabsorption of glucose filtrated through glomerular (J. Clin. Invest., Vol.93, pp.397-404 (1994)). Accordingly, inhibiting a human SGLT2 activity prevents reabsorption of excess glucose at the kidney, subsequently promotes excreting excess glucose though the urine, and normalizes blood glucose level. Therefore, fast development of antidiabetic agents, which have a potent inhibitory activity in human SGLT2 and have a new mechanism, has been desired. Also, since such agents promote the excretion of excess glucose though the urine and consequently the glucose accumulation in the body is decreased, they are also expected to have a preventing or alleviating effect on obesity.

[0004] As compounds having pyrazole moiety, it is described that WAY-123783 increased the amount of excreted glucose in normal mice. However, its effects in humans are not described at all (J. Med. Chem., Vol. 39, pp. 3920-3928 (1996)).

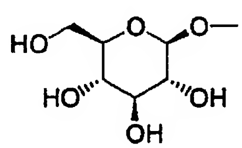
Disclosure of the Invention

[0005] The present invention relates to a glucopyranosyloxypyrazole derivative represented by the general formula:



(I)

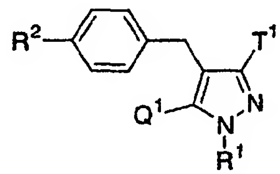
wherein R^1 represents a hydrogen atom or a lower alkyl group; one of Q^1 and T^1 represents a group represented by the formula:



while the other represents a lower alkyl group or a halo(lower alkyl) group; and R^2 represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom, or a pharmaceutically acceptable salt thereof.

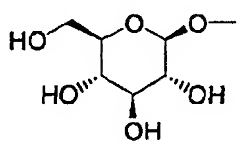
[0006] Also, the present invention relates to a pharmaceutical composition which comprise as an active ingredient

a glucopyranosyloxypyrazole derivative represented by the general formula:



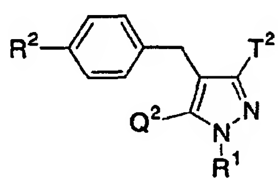
(I)

wherein R^1 represents a hydrogen atom or a lower alkyl group; one of Q^1 and T^1 represents a group represented by the formula:



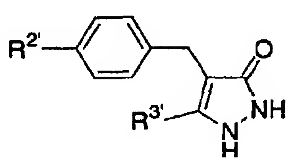
while the other represents a lower alkyl group or a halo(lower alkyl) group; and R^2 represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom, or a pharmaceutically acceptable salt thereof.

[0007] Furthermore, The present invention relates to a glucopyranosyloxypyrazole derivative represented by the general formula:



(VII)

wherein R^1 represents a hydrogen atom or a lower alkyl group; one of Q^2 and T^2 represents a 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy group, while the other represents a lower alkyl group or a halo(lower alkyl) group; and R^2 represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom, or a salt thereof, and to a benzylpyrazole derivative represented by the general formula:



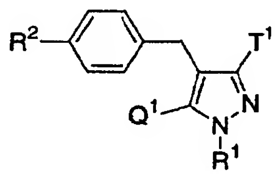
(Va)

wherein $R^{2'}$ represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom; and $R^{3'}$ represents a lower alkyl group, or a salt thereof.

Best Mode for Carrying Out the Invention

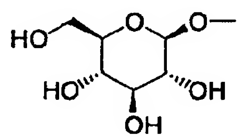
[0008] The present inventors have studied earnestly to find compounds having inhibitory activity in human SGLT2. As a result, it was found that glucopyranosyloxypyrazole derivatives represented by the above general formula (I) exhibit excellent inhibitory activity in human SGLT2 as mentioned below, thereby forming the basis of the present invention.

[0009] This is, the present invention relates to a glucopyranosyloxypyrazole derivative represented by the general formula:



(I)

wherein R^1 represents a hydrogen atom or a lower alkyl group; one of Q^1 and T^1 represents a group represented by the formula:

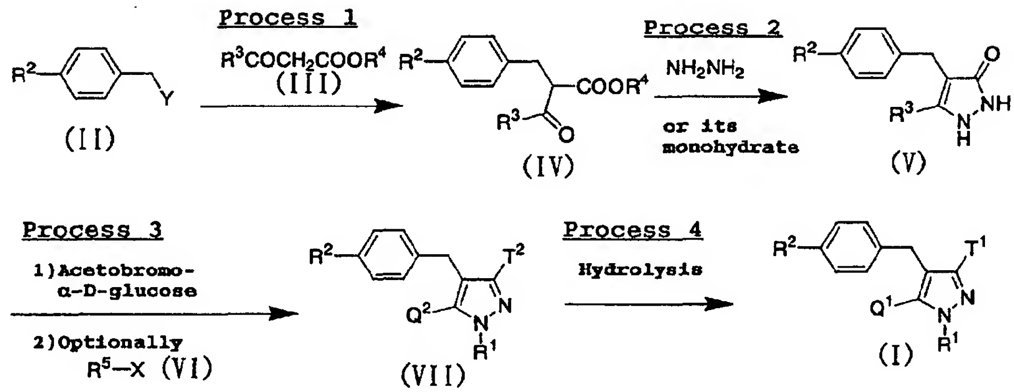


while the other represents a lower alkyl group or a halo(lower alkyl) group; and R^2 represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom, or a pharmaceutically acceptable salt thereof, a pharmaceutical composition comprising the same and an intermediate thereof.

[0010] In the compounds represented by the above general formula (I), the term "lower alkyl group" means a straight-chained or branched alkyl group having 1 to 6 carbon atoms such as a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a *sec*-butyl group, a *tert*-butyl group, a pentyl group, an isopentyl group, a neopentyl group, a *tert*-pentyl group, a hexyl group or the like; the term "lower alkoxy group" means a straight-chained or branched alkoxy group having 1 to 6 carbon atoms such as a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, an isobutoxy group, a *sec*-butoxy group, a *tert*-butoxy group, a pentyloxy group, an isopentyloxy group, a neopentyloxy group, a *tert*-pentyloxy group, a hexyloxy group or the like; and the term "lower alkylthio group" means a straight-chained or branched alkylthio group having 1 to 6 carbon atoms such as a methylthio group, an ethylthio group, a propylthio group, an isopropylthio group, a butylthio group, an isobutylthio group, a *sec*-butylthio group, a *tert*-butylthio group, a pentylthio group, an isopentylthio group, a neopentylthio group, a tert-pentylthio group, a hexylthio group or the like. The term "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom; and the term "halo(lower alkyl) group" means the above lower alkyl group substituted by different or same 1 to 3 halogen atoms as defined above.

[0011] In the substituent R^1, a hydrogen atom or a straight-chained or branched alkyl group having 1 to 3 carbon atoms are preferable; and a hydrogen atom, an ethyl group, a propyl group or an isopropyl group are more preferable. In the substituent R^2, a straight-chained or branched alkyl group having 1 to 4 carbon atoms, a straight-chained or branched alkoxy group having 1 to 3 carbon atoms, or a straight-chained or branched alkylthio group having 1 to 3 carbon atoms are preferable; and an ethyl group, an ethoxy group, an isopropoxy group or a methylthio group are more preferable. In the substituents Q^1 and T^1, it is preferable that either of them is a straight-chained or branched alkyl group having 1 to 3 carbon atoms, and it is more preferable that either of them is a methyl group.

[0012] For example, the compounds represented by the above general formula (I) of the present invention can be prepared according to the following procedure:



wherein X and Y represent a leaving group such as a halogen atom, a mesyloxy group or a tosyloxy group; R^3 represents a lower alkyl group or a halo(lower alkyl) group; R^4 represents a methyl group or an ethyl group; R^5 represents a lower alkyl group; one of Q^2 and T^2 represents a 2,3,4,6-tetra-O-acetyl-β-D-gluco-pyranosyloxy group, while the other represents a lower alkyl group or a halo(lower alkyl) group; and R^1, R^2, Q^1 and T^1 have the same meanings as defined above.

Process 1

[0013] A compound represented by the above general formula (IV) can be prepared by condensing a benzyl derivative represented by the above general formula (II) with a ketoacetate represented by the above general formula (III) in the presence of a base such as sodium hydride or potassium *tert*-butoxide in an inert solvent. As the inert solvent used in the reaction, 1,2-dimethoxyethane, tetrahydrofuran, *N,N*-dimethylformamide, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on a used starting material, solvent and reaction temperature.

Process 2

[0014] A pyrazolone derivative represented by the above general formula (V) can be prepared by condensing a compound represented by the above general formula (IV) with hydrazine or hydrazine monohydrate in an inert solvent. As the inert solvent used in the reaction, toluene, tetrahydrofuran, chloroform, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on a used starting material, solvent and reaction temperature. The obtained pyrazolone derivative represented by the above general formula (V) can be also used in process 3 after converting into a salt thereof in usual way.

Process 3

[0015]

(1) In case of pyrazolone derivatives represented by the above general formula (V) wherein R^3 is a lower alkyl group, a corresponding compound represented by the above general formula (VII) can be prepared by subjecting a corresponding pyrazolone derivative represented by the above general formula (V) to glycosidation using acetobromo-α-D-glucose in the presence of a base such as silver carbonate in an inert solvent, and subjecting the resulting compound to *N*-alkylation using an alkylating agent represented by the above general formula (VI) in the presence of a base such as pottasium carbonate in an inert solvent as occasion demands. As the solvent used in the glycosidation reaction, tetrohydrofuran and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, depending on the starting material, solvent and reaction temperature used. As the solvent used in the N-alkylation reaction, acetonitrile, *N,N*-dimethylformamide, tetrohydrofuran, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from room terperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, depending on the starting material, solvent and reaction temperature used.

(2) In the case of pyrazolone derivatives represented by the above general formula (V) wherein R^3 is a halo(lower

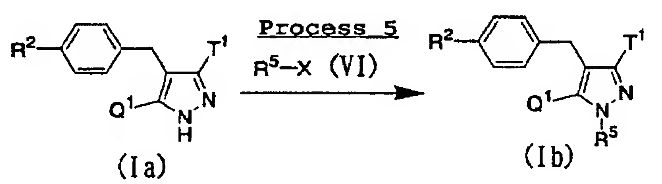
alkyl) group, a corresponding compound represented by the above general formula (VII) can be prepared by subjecting a corresponding pyrazolone derivative represented by the above general formula (V) to glycosidation using acetobromo-α-D-glucose in the presence of a base such as potassium carbonate in an inert solvent, and subjecting the resulting compound to *N*-alkylation using an alkylating agent represented by the above general formula (VI) in the presence of a base such as potassium carbonate in an inert solvent as occasion demands. As the solvent used in the glycosidation reaction, acetonitrile, tetrohydrofuran and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, depending on the starting material, solvent and reaction temperature used. As the solvent used in the *N*-alkylation reaction, acetonitrile, *N,N*-dimethylformamide, tetrohydrofuran, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, depending on the starting material, solvent and reaction temperature used.

[0016] The obtained compounds represented by the above general formula (VII) can be also used in process 4 after converting into a salt thereof in a usual way.

Process 4

[0017] A compound (I) of the present invention can be prepared by subjecting a compound represented by the above general formula (VII) to alkaline hydrolysis. As the solvent used in the reaction, methanol, ethanol, tetrahydrofuran, water, a mixed solvent thereof and the like can be illustrated, and as the base used, sodium hydroxide, sodium ethoxide and the like can be illustrated. The reaction temperature is usually from 0°C to room temperature, and the reaction time is usually from 30 minutes to 6 hours, depending on the starting material, solvent and reaction temperature used.

[0018] Of the compounds represented by the above general formula (I), compounds wherein the substituent R^1 is a lower alkyl group can be prepared according to the following procedure:



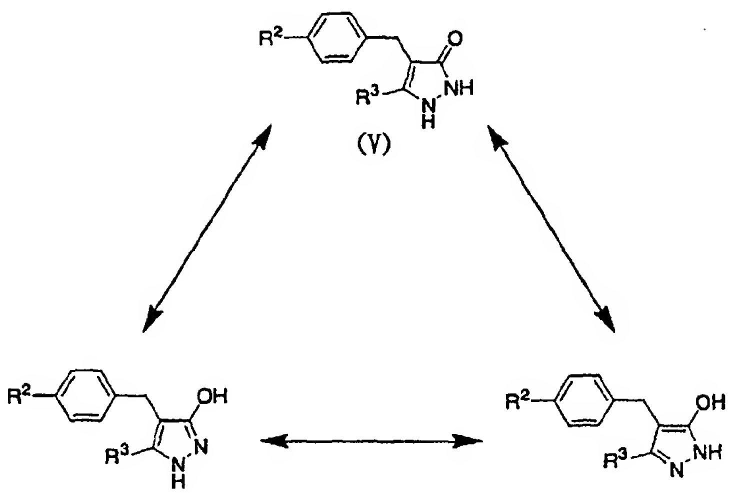
wherein Q^1, R^2, R^5, T^1 and X have the same meanings as defined above.

Process 5

[0019] A compound represented by the above general formula (Ib) of the present invention can be prepared by subjecting a compound represented by the above general formula (Ia) of the present invention to *N*-alkylation using an *N*-alkylating agent represented by the above general formula (VI) in the presence of a base such as potassium carbonate or cesium carbonate, and occasionally a catalytic amount of sodium iodide in an inert solvent. As the inert solvent used in the reaction, *N,N*-dimethylformamide, dimethoxyethane, dimethyl sulfoxide, tetrahydrofuran, ethanol, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 10 minutes to 1 day, depending on the starting material, solvent and reaction temperature used.

[0020] The compounds represented by the above general formula (VII) and salts thereof which are used in the aforementioned production process are compounds useful as intermediates of compounds represented by the above general formula (I) of the present invention. In the compounds represented by the above general formula (VII) as well as the compounds represented by the above general formula (I) of the present invention, it is preferable that either of the substituents Q^2 and T^2 is a straight-chained or branched alkyl group having 1 to 3 carbon atoms, and it is more preferable that either of them is a methyl group.

[0021] In the compound represented by the above general formula (V) as starting materials, there are the following three tautomers, depending on the change of reaction conditions:



wherein R^2 and R^3 have the same meanings as defined above. The compounds represented by the above general formula (V) and salts thereof which are used in the aforementioned production process are compounds useful as intermediates of compounds represented by the above general formula (I) of the present invention. In the compounds represented by the above general formula (V) as well as the compounds represented by the above general formula (I) of the present invention, it is preferable that the substituent R^3 is a straight-chained or branched alkyl group having 1 to 3 carbon atoms, and it is more preferable that the substituent R^3 is a methyl group.

[0022] The compounds represented by the above general formula (I) of the present invention obtained by the above production processes can be isolated and purified by conventional separation means such as fractional recrystallization, purification using chromatography and solvent extraction.

[0023] The glucopyranosyloxypyrazole derivatives represented by the above general formula (I) of the present invention can be converted into their pharmaceutically acceptable salts in the usual way. Examples of such salts include acid addition salts with mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid and the like, acid addition salts with organic acids such as formic acid, acetic acid, methanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, propionic acid, citric acid, succinic acid, tartaric acid, fumaric acid, butyric acid, oxalic acid, malonic acid, maleic acid, lactic acid, malic acid, carbonic acid, glutamic acid, aspartic acid and the like, and salts with inorganic bases such as a sodium salt, a potassium salt and the like.

[0024] The compounds represented by the above general formula (I) of the present invention include their their solvates with pharmaceutically acceptable solvents such as ethanol and water.

[0025] The compounds represented by the above general formula (I) of the present invention have excellent inhibitory activity on human SGLT2 and are extremely useful as agents for the prevention or treatment of diabetes, diabetic complications, obesity and the like. For example, in the following assay for inhibitory effect on human SGLT2 activity, the compounds of the present invention exerted a potent inhibitory activity on human SGLT2. On the other hand, since WAY-123783 has an extremely weak inhibitory activity on human SGLT2, it cannot be expected to exert a sufficient effect as a human SGLT2 inhibitor.

[0026] When the pharmaceutical compositions of the present invention are employed in practical treatment, various dosage forms are used depending on their uses. As examples of the dosage forms, powders, granules, fine granules, dry syrups, tablets, capsules, injections, solutions, ointments, suppositories, poultices and the like are illustrated, which are orally or parenterally administered.

[0027] These pharmaceutical compositions can be prepared by admixing with or by diluting and dissolving an appropriate pharmaceutical additive such as excipients, disintegrators, binders, lubricants, diluents, buffers, isotonicities, antiseptics, moistening agents, emulsifiers, dispersing agents, stabilizing agents, dissolving aids and the like, and formulating the mixture in the conventional manner.

[0028] When the pharmaceutical compositions of the present invention are employed in practical treatment, the dosage of a compound represented by the above general formula (I) or a pharmaceutically acceptable salt thereof as the active ingredient is appropriately decided depending on the age, sex, body weight and degree of symptoms and treatment of each patient, which is approximately within the range of from 0.1 to 1,000mg per day per adult human in the case of oral administration and approximately within the range of from 0.01 to 300mg per day per adult human in the case of parenteral administration, and the daily dose can be divided into several doses per day and administered suitably.

Examples

[0029] The present invention is further illustrated in more detail by way of the following Reference Examples, Examples and Test Examples. However, the present invention is not limited thereto.

Example 1

1,2-Dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one

[0030] To a solution of 4-isopropoxybenzylalcohol (0.34g) in tetrahydrofuran (6mL) were added triethylamine (0.28mL) and methanesulfonyl chloride (0.16mL), and the mixture was stirred at room temperature for 30 minutes. The resulting insoluble material was removed by filtration. The obtained solution of 4-isopropoxybenzyl methanesulfonate in tetrahydrofuran was added to a suspension of sodium hydride (60%, 81mg) and methyl acetoacetate (0.20mL) in 1,2-dimethoxyethane (10mL), and the mixture was stirred at 80°C overnight. The reaction mixture was poured into a saturated aqueous sodium hydrogen carbonate solution, and the resulting mixture was extracted with diethyl ether. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was dissolved in toluene (5mL). Anhydrous hydrazine (0.19mL) was added to the solution, and the mixture was stirred at 80°C overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to give 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3H-pyrazol-3-one (95mg).
^{1}H-NMR (500MHz, DMSO-d_6) δ ppm:
1.22 (6H, d, J=6.0Hz), 1.99 (3H, s), 3.45 (2H, s), 4.40-4.60 (1H, m), 6.65-6.80 (2H, m), 6.95-7.10 (2H, m)

Example 2

1,2-Dihydro-5-methyl-4-[(4-propylphenyl)methyl]-3*H*-pyrazol-3-one

[0031] The title compound was prepared in a similar manner to that described in Example 1 using 4-propylbenzyl alcohol instead of 4-isopropoxybenzyl alcohol.
^{1}H-NMR (500MHz, DMSO-d_6) δ ppm:
0.75-0.95 (3H, m), 1.45-1.65 (2H, m), 1.99 (3H, s), 2.40-2.55 (2H, m), 3.32 (2H, s), 6.95-7.10 (4H, m)

Example 3

1,2-Dihydro-4-[(4-isobutylphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one

[0032] The title compound was prepared in a similar manner to that described in Example 1 using 4-isobutylbenzyl alcohol instead of 4-isopropoxybenzyl alcohol.
^{1}H-NMR (500MHz, DMSO-d_6) δ ppm:
0.83 (6H, d, J=6.6Hz), 1.70-1.85 (1H, m), 1.99 (3H, s), 2.30-2.45 (2H, m), 3.50 (2H, s), 6.90-7.10 (4H, m)

Example 4

1,2-Dihydro-5-methyl-4-[(4-propoxyphenyl)methyl]-3*H*-pyrazol-3-one

[0033] The title compound was prepared in a similar manner to that described in Example 1 using 4-propoxybenzyl alcohol instead of 4-isopropoxybenzyl alcohol.
^{1}H-MMR (500MHz, DMSO-d_6) δ ppm:
0.95 (3H, t, J=7.4Hz), 1.60-1.75 (2H, m), 1.98 (3H, s), 3.46 (2H, s), 3.75-3.90 (2H, m), 6.70-6.85 (2H, m), 6.95-7.10 (2H, m)

Example 5

4-[(4-Ethoxyphenyl)methyl]-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one

[0034] The title compound was prepared in a similar manner to that described in Example 1 using 4-ethoxybenzyl alcohol instead of 4-isopropoxybenzyl alcohol.
^{1}H-NMR (500MHz, DMSO-d_6) δ ppm:

1.20-1.35 (3H, m), 1.98 (3H, s), 3.46 (2H, s), 3.85-4.05 (2H, m), 6.70-6.85 (2H, m), 6.95-7.10 (2H, m)

Example 6

1,2- Dihydro-5-methyl-4-[(4-trifluoromethylphenyl)methyl]-3*H*-pyrazol-3-one

[0035] The title compound was prepared in a similar manner to that described in Example 1 using 4-trifluoromethylbenzyl alcohol instead of 4-isopropoxybenzyl alcohol.
^{1}H-NMR (500MHz, DMSO-d_6) δ ppm:
2.02 (3H, s), 3.64 (2H, s), 7.30-7.45 (2H, m), 7.55-7.70 (2H, m)

Example 7

4-[(4-*tert*-Butylphenyl)methyl]-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one

[0036] The title compound was prepared in a similar manner to that described in Example 1 using 4-tert-butylbenzyl alcohol instead of 4-isopropoxybenzyl alcohol.
^{1}H-NMR (500MHz, DMSO-d_6) δ ppm:
1.24 (9H, s), 2.01 (3H, s), 3.49 (2H, s), 7.00-7.15 (2H, m), 7.15-7.30 (2H, m)

Example 8

4-[(4-Butoxyphenyl)methyl]-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one

[0037] The title compound was prepared in a similar manner to that described in Example 1 using 4-butoxybenzyl alcohol instead of 4-isopropoxybenzyl alcohol.
^{1}H-NMR (500MHz, DMSO-d_6) δ ppm:
0.91 (3H, t, J=7.4Hz), 1.30-1.50 (2H, m), 1.55-1.75 (2H, m), 1.98 (3H, s), 3.46 (2H, s), 3.80-3.95 (2H, m), 6.70-6.85 (2H, m), 6.95-7.10 (2H, m)

Example 9

1,2-Dihydro-5-methyl-4-[(4-methylthiophenyl)methyl]-3*H*-pyrazol-3-one

[0038] The title compound was prepared in a similar manner to that described in Example 1 using 4-(methylthio) benzyl alcohol instead of 4-isopropoxybenzyl alcohol.
^{1}H-NMR (500MHz, DMSO-d_6) δ ppm:
1.99 (3H, s), 2.42 (3H, s), 3.50 (2H, s), 7.05-7.20 (4H, m)

Example 10

5-Ethyl-1,2-dihydro-4-[(4-methylthiophenyl)methyl]-3*H*-pyrazol-3-one

[0039] The title compound was prepared in a similar manner to that described in Example 1 using 4-(methylthio) benzyl alcohol instead of 4-isopropoxybenzyl alcohol and using methyl 3-oxopentanoate instead of methyl acetoacetate.
^{1}H-NMR (500MHz, DMSO-d_6) δ ppm:
1.02 (3H, t, J=7.6Hz), 2.39 (2H, q, J=7.6Hz), 2.42 (3H, s), 3.51 (2H, s), 7.05-7.20 (4H, m)

Example 11

1,2-Dihydro-4-[(4-isopropylphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one

[0040] To a suspension of sodium hydride (60%, 40mg) in 1,2-dimethoxyethane (1mL) were added methyl acetoacetate (0.11mL), 4-isopropylbenzyl chloride (0.17g) and a catalytic amount of sodium iodide, and the mixture was stirred at 80°C overnight. The reaction mixture was poured into a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with diethyl ether. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was dissolved in toluene (1mL).

Anhydrous hydrazine (0.094mL) was added to the solution, and the mixture was stirred at 80°C overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to give 1,2-dihydro-4-[(4-isopropylphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one (0.12g).
^{1}H-NMR (500MHz, DMSO-d_6) δ ppm:
1.16 (6H, d, J=6.9Hz), 2.01 (3H, s), 2.70-2.90 (1H, m), 3.49 (2H, s), 6.95-7.20 (4H, m)

Example 12

4-[(4-Ethylphenyl)methyl]-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one

[0041] The title compound was prepared in a similar manner to that described in Example 11 using 4-ethylbenzyl chloride instead of 4-isopropylbenzyl chloride.
^{1}H-NMR (500MHz, DMSO-d_6) δ ppm:
1.13 (3H, t, J=7.6Hz), 2.00 (3H, s), 2.45-2.60 (2H, m), 3.49 (2H, s), 7.00-7.15 (4H, m)

Example 13

1,2-Dihydro-5-methyl-4-[(4-methylphenyl)methyl]-3*H*-pyrazol-3-one

[0042] The title compound was prepared in a similar manner to that described in Example 11 using 4-methylbenzyl bromide instead of 4-isopropylbenzyl chloride.
^{1}H-NMR (500MHz, DMSO-d_6) δ ppm:
1.98 (3H, s), 2.23 (3H, s), 3.48 (2H, s), 6.95-7.10 (4H, m)

Reference Example 1

4-Benzyl-1,2-dihydro-5-trifluoromethyl-3*H*-pyrazol-3-one

[0043] The title compound was prepared in a similar manner to that described in Example 11 using ethyl trifluoroacetoacetate instead of methyl acetoacetate and using benzyl bromide instead of 4-isopropylbenzyl chloride.
^{1}H-NMR (500MHz, DMSO-d_6) δ ppm:
3.73 (2H, s), 7.05-7.35 (5H, m), 12.50-13.10 (1H, brs)

Example 14

1,2-Dihydro-4-[(4-methoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one

[0044] The title compound was prepared in a similar manner to that described in Example 11 using 4-methoxybenzyl bromide instead of 4-isopropylbenzyl chloride.
^{1}H-NMR (500MHz, DMSO-d_6) δ ppm:
1.99 (3H, s), 3.47 (2H, s), 3.69 (3H, s), 6.75-6.85 (2H, m), 7.00-7.10 (2H, m), 8.70-11.70 (2H, br)

Reference Example 2

4-Benzyl-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one

[0045] The title compound was prepared in a similar manner to that described in Example 11 using benzyl bromide instead of 4-isopropylbenzyl chloride.
^{1}H-NMR (500MHz, DMSO-d_6) δ ppm:
2.00 (3H, s), 3.54 (2H, s), 7.05-7.30 (5H, s)

Example 15

4-[(4-Isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

[0046] To a suspension of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one (46mg), acetobromo-α-D-glucose (99mg) and 4A molecular sieves in tetrahydrofuran (3mL) was added silver carbonate (66mg), and

the mixture was stirred under shading the light at 65°C overnight. The reaction mixture was purified by column chromatography on aminopropyl silica gel (eluent: tetrahydrofuran). Further purification by preparative thin layer chromatography on silica gel (developing solvent: ethyl acetate/hexane = 2/1) afforded 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (42mg).
^{1}H-NMR (500MHz, $CDCl_3$) δ ppm:
1.25-1.35 (6H, m), 1.88 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 3.45-3.65 (2H, m), 3.80-3.90 (1H, m), 4.13 (1H, dd, J=2.3, 12.4Hz), 4.31 (1H, dd, J=4.0, 12.4Hz), 4.40-4.55 (1H, m), 5.15-5.35 (3H, m), 5.50-5.60 (1H, m), 6.70-6.80 (2H, m), 6.95-7.05 (2H, m)

Example 16

5-Methyl-4-[(4-propylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

[0047] The title compound was prepared in a similar manner to that described in Example 15 using 1,2-dihydro-5-methyl-4-[(4-propylphenyl)methyl]-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.
^{1}H-NMR (500MHz, $CDCl_3$) δ ppm:
0.91 (3H, t, J=7.3Hz), 1.50-1.65 (2H, m), 1.86 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 2.45-2.55 (2H, m), 3.55 (1H, d, J=15.8Hz), 3.63 (1H, d, J=15.8Hz), 3.80-3.90 (1H, m), 4.13 (1H, dd, J=2.3, 12.4Hz), 4.30 (1H, dd, J=3.9, 12.4Hz), 5.15-5.35 (3H, m), 5.50-5.60 (1H, m), 7.00-7.20 (4H, m)

Example 17

4-[(4-Isobutylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

[0048] The title compound was prepared in a similar manner to that described in Example 15 using 1,2-dihydro-4-[(4-isobutylphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.
^{1}H-NMR (500MHz, $CDCl_3$) δ ppm:
0.87 (6H, d, J=6.6Hz), 1.70-1.85 (1H, m), 1.87 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 2.40 (2H, d, J=7.2Hz), 3.56 (1H, d, J=15.8Hz), 3.63 (1H, d, J=15.8Hz), 3.80-3.90 (1H, m), 4.14 (1H, dd, J=2.3, 12.4Hz), 4.31 (1H, dd, J=4.0, 12.4Hz), 5.15-5.35 (3H, m), 5.50-5.60 (1H, m), 6.95-7.10 (4H, m)

Example 18

5-Methyl-4-[(4-propoxyphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

[0049] The title compound was prepared in a similar manner to that described in Example 15 using 1,2-dihydro-5-methyl-4-[(4-propoxyphenyl)methyl]-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.
^{1}H-NMR (500MHz, $CDCl_3$) δ ppm:
1.01 (3H, t, J=7.4Hz), 1.70-1.85 (2H, m), 1.89 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 3.53 (1H, d, J=15.7Hz), 3.59 (1H, d, J=15.7Hz), 3.80-3.95 (3H, m), 4.14 (1H, dd, J=2.3, 12.4Hz), 4.31 (1H, dd, J=4.0, 12.4Hz), 5.15-5.35 (3H, m), 5.50-5.60 (1H, m), 6.70-6.80 (2H, m), 6.95-7.10 (2H, m)

Example 19

4-[(4-Ethoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

[0050] The title compound was prepared in a similar manner to that described in Example 15 using 4-[(4-ethoxyphenyl)-methyl]-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.
^{1}H-NMR (500MHz, $CDCl_3$) δ ppm:
1.38 (3H, t, J=7.0Hz), 1.89 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 3.53 (1H, d, J=15.8Hz), 3.59 (1H, d, J=15.8Hz), 3.80-3.90 (1H, m), 3.98 (2H, q, J=7.0Hz), 4.13 (1H, dd, J=2.3, 12.4Hz), 4.31 (1H, dd, J=4.0, 12.4), 5.15-5.30 (3H, m), 5.50-5.60 (1H, m), 6.70-6.80 (2H, m), 6.95-7.10 (2H, m)

Example 20

5-Methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-4-[(4-trifluoromethylphenyl)methyl]-1*H*-pyrazole

[0051] The title compound was prepared in a similar manner to that described in Example 15 using 1,2-dihydro-5-methyl-4-[(4-trifluoromethylphenyl)methyl]-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.
^{1}H-NMR (500MHz, $CDCl_3$) δ ppm:
1.85 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.14 (3H, s), 3.65 (1H, d, J=15.9Hz), 3.71 (1H, d, J=15.9Hz), 3.80-3.90 (1H, m), 4.14 (1H, dd, J=2.4, 12.4Hz), 4.31 (1H, dd, J=4.0, 12.4Hz), 5.15-5.40 (3H, m), 5.55-5.65 (1H, m), 7.20-7.30 (2H, m), 7.45-7.55 (2H, m)

Example 21

4-[(4-*tert*-Butylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

[0052] The title compound was prepared in a similar manner to that described in Example 15 using 4-[(4-*tert*-butylphenyl)-methyl]-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.
^{1}H-NMR (500MHz, $CDCl_3$) δ ppm:
1.27 (9H, s), 1.84 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.14 (3H, s), 3.56 (1H, d, J=15.8Hz), 3.64 (1H, d, J=15.8Hz), 3.80-3.90 (1H, m), 4.13 (1H, dd, J=2.3, 12.4Hz), 4.31 (1H, dd, J=4.0, 12.4Hz), 5.15-5.30 (3H, m), 5.50-5.60 (1H, m), 7.00-7.10 (2H, m), 7.20-7.30 (2H, m)

Example 22

4-[(4-Butoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O* acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

[0053] The title compound was prepared in a similar manner to that described in Example 15 using 4-[(4-butoxyphenyl)-methyl]-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3H-pyrazol-3-one.
^{1}H-NMR (500MHz, $CDCl_3$) δ ppm:
0.96 (3H, t, J=7.4Hz), 1.40-1.55 (2H, m), 1.65-1.80 (2H, m), 1.88 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 3.52 (1H, d, J=15.8Hz), 3.59 (1H, d, J=15.8Hz), 3.80-3.90 (1H, m), 3.91 (2H, t, J=6.5Hz), 4.13 (1H, dd, J=2.3, 12.4Hz), 4.31 (1H, dd, J=4.0, 12.4Hz), 5.15-5.30 (3H, m), 5.50-5.60 (1H, m), 6.70-6.80 (2H, m), 6.95-7.10 (2H, m)

Example 23

5-Methyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

[0054] The title compound was prepared in a similar manner to that described in Example 15 using 1,2-dihydro-5-methyl-4-[(4-methylthiophenyl)methyl]-3H-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3H-pyrazol-3-one.
^{1}H-NMR (500MHz, $CDCl_3$) δ ppm:
1.88 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.07 (3H, s), 2.12 (3H, s), 2.44 (3H, s), 3.50-3.65 (2H, m), 3.80-3.90 (1H, m), 4.13 (1H, dd, J=2.4, 12.4Hz), 4.31 (1H, dd, J=4.1, 12.4Hz), 5.15-5.30 (3H, m), 5.55-5.65 (1H, m), 7.00-7.10 (2H, m), 7.10-7.20 (2H, m), 8.65-8.85 (1H, brs)

Example 24

5-Ethyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

[0055] The title compound was prepared in a similar manner to that described in Example 15 using 5-ethyl-1,2-dihydro-4-[(4-methylthiophenyl)methyl]-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.
^{1}H-NMR (500MHz, $CDCl_3$) δ ppm:
1.13 (3H, t, J=7.6Hz), 1.88 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.44 (3H, s), 2.45-2.55 (2H, m), 3.50-3.70 (2H, m), 3.80-3.90 (1H, m), 4.05-4.20 (1H, m), 4.31 (1H, dd, J=4.0, 12.4Hz), 5.15-5.35 (3H, m), 5.55-5.65 (1H, m),

7.00-7.10 (2H, m), 7.10-7.20 (2H, m), 8.80-9.20 (1H, brs)

Example 25

4-[(4-Isopropylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

[0056] The title compound was prepared in a similar manner to that described in Example 15 using 1,2-dihydro-4-[(4-isopropylphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.
^{1}H-NMR (500MHz, $CDCl_3$) δ ppm:
1.20 (6H, d, J=6.9Hz), 1.85 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.13 (3H, s), 2.75-2.90 (1H, m), 3.56 (1H, d, J=15.8Hz), 3.63 (1H, d, J=15.8Hz), 3.80-3.90 (1H, m), 4.05-4.20 (1H, m), 4.31 (1H, dd, J=4.0, 12.4Hz), 5.15-5.35 (3H, m), 5.50-5.60 (1H, m), 7.00-7.15 (4H, m), 8.70-9.30 (1H, brs)

Example 26

4-[(4-Methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole

[0057] To a solution of 1,2-dihydro-4-[(4-methylthiophenyl)-methyl]-5-trifluoromethyl-3*H*-pyrazol-3-one (2.0g) in acetonitrile (100mL) were added acetobromo-α-D-glucose (3.1g) and potassium carbonate (1.1g), and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 1/1) to give 4-[(4-methylthiophenyl) methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole (2.0g).
^{1}H-NMR (500MHz, $CDCl_3$) δ ppm:
1.91 (3H, s), 2.03 (3H, s), 2.04 (3H, s), 2.09 (3H, s), 2.45 (3H, s), 3.73 (2H, s), 3.75-3.90 (1H, m), 4.15-4.35 (2H, m), 5.15-5.65 (4H, m), 7.00-7.20 (4H, m)

Example 27

4-Benzyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole

[0058] The title compound was prepared in a similar manner to that described in Example 26 using 4-benzyl-1,2-dihydro-5-trifluoromethyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-3*H*-pyrazol-3-one.
^{1}H-NMR (500MHz, $CDCl_3$) δ ppm:
1.89 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.08 (3H, s), 3.70-3.90 (3H, m), 4.15-4.30 (2H, m), 5.10-5.50 (4H, m), 7.10-7.30 (5H, m)

Example 28

4-[(4-Methoxyphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole

[0059] The title compound was prepared in a similar manner to that described in Example 26 using 1,2-dihydro-4-[(4-methoxyphenyl)methyl]-5-trifluoromethyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-3*H*-pyrazol-3-one.
^{1}H-NMR (400MHz, $CDCl_3$) δ ppm:
1.93 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.09 (3H, s), 3.65-3.75 (2H, m), 3.77 (3H, s), 3.75-3.90 (1H, m), 4.15-4.35 (2H, m), 5.10-5.45 (4H, m), 6.75-6.85 (2H, m), 7.00-7.15 (2H, m)

Example 29

4-[(4-Methoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

[0060] The title compound was prepared in a similar manner to that described in Example 15 using 1,2-dihydro-4-[(4-methoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.

^1H-NMR (400MHz, $CDCl_3$) δ ppm:
1.89 (3H, s), 2.02 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 3.45-3.65 (2H, m), 3.76 (3H, s), 3.80-3.90 (1H, m), 4.11 (1H, dd, J=2.2, 12.4Hz), 4.30 (1H, dd, J=4.0, 12.4Hz), 5.15-5.35 (3H, m), 5.50-5.60 (1H, m), 6.70-6.85 (2H, m), 7.00-7.10 (2H, m)

Example 30

4-Benzyl-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

[0061] The title compound was prepared in a similar manner to that described in Example 15 using 4-benzyl-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.
^1H-NMR (400MHz, $CDCl_3$) δ ppm:
1.86 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.11 (3H, s), 3.59 (1H, d, J=15.8Hz), 3.66 (1H, d, J=15.8Hz), 3.80-3.90 (1H, m), 4.11 (1H, dd, J=2.3, 12.4Hz), 4.30 (1H, dd, J=4.0, 12.4Hz), 5.15-5.30 (3H, m), 5.50-5.65 (1H, m), 7.05-7.30 (5H, m), 8.75-9.55 (1H, brs)

Example 31

4-[(4-Methoxyphenyl)methyl]-1,5-dimethyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)pyrazole

[0062] A suspension of 4-[(4-methoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (18mg), potassium carbonate (14mg) and iodomethane (4.7mg) in acetonitrile (2mL) was stirred at 75°C overnight. The reaction mixture was filtered through celite®, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by preparative thin layer chromatography (developing solvent: benzene/acetone = 2/1) to give 4-[(4-methoxyphenyl)methyl]-1,5-dimethyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)pyrazole (4mg).
^1H-NMR (500MHz, $CDCl_3$) δ ppm:
1.90 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.07 (3H, s), 3.45-3.60 (2H, m), 3.60 (3H, s), 3.76 (3H, s), 3.80-3.90 (1H, m), 4.13 (1H, dd, J=2.4, 12.4Hz), 4.29 (1H, dd, J=4.1, 12.4Hz), 5.15-5.30 (3H, m), 5.50-5.60 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

Example 32

1-Methyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethylpyrazole

[0063] A suspension of 4-[(4-metylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole (30mg), potassium carbonate (8.0mg) and iodomethane (8.2mg) in tetrahydrofuran (1mL) was stirred at 75°C overnight. The reaction mixture was filtered through celite®, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by preparative thin layer chromatography (developing solvent: dichloromethane/ethyl acetate = 5/1) to give 1-methyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethylpyrazole (13mg).
^1H-NMR (500MHz, $CDCl_3$) δ ppm:
1.89 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 2.44 (3H, s), 3.65-3.95 (6H, m), 4.14 (1H, dd, J=2.3, 12.4Hz), 4.29 (1H, dd, J=4.3, 12.4Hz), 5.15-5.35 (3H, m), 5.50-5.65 (1H, m), 7.00-7.20 (4H, m)

Example 33

1-Ethyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethylpyrazole

[0064] The title compound was prepared in a similar manner to that described in Example 32 using iodoethane instead of iodomethane.
^1H-NMR (500MHz, $CDCl_3$) δ ppm:
1.40 (3H, t, J=7.2Hz), 1.90 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 2.44 (3H, s), 3.72 (2H, s), 3.80-3.90 (1H, m), 4.05-4.20 (3H, m), 4.27 (1H, dd, J=4.5, 12.4Hz), 5.10-5.35 (3H, m), 5.55-5.65 (1H, m), 7.00-7.10 (2H, m), 7.10-7.20 (2H, m)

Example 34

4-[(4-Methylthiophenyl)methyl]-1-propyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethylpyrazole

[0065] The title compound was prepared in a similar manner to that described in Example 32 using iodopropane instead of iodomethane.
^{1}H-NMR (500MHz, $CDCl_3$) δ ppm:
0.92 (3H, t, J=7.4Hz), 1.75-1.90 (2H, m), 1.89 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 2.44 (3H, s), 3.72 (2H, s), 3.80-3.90 (1H, m), 3.90-4.05 (2H, m), 4.12 (1H, dd, J=2.3, 12.4Hz), 4.27 (1H, dd, J=4.5, 12.4Hz), 5.10-5.35 (3H, m), 5.55-5.65 (1H, m), 7.00-7.10 (2H, m), 7.10-7.20 (2H, m)

Example 35

3-(β-D-Glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole

[0066] To a solution of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (61mg) in ethanol (3mL) was added 1N aqueous sodium hydroxide solution (0.53mL), and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure, and the residue was purified by solid phase extraction on ODS (washing solvent: distilled water, eluent: methanol) to give 3-(β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)-methyl]-5-methyl-1*H*-pyrazole (39mg).
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
1.26 (6H, d, J=5.9Hz), 2.05 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.75-3.90 (1H, m), 4.45-4.60 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.15 (2H, m)

Example 36

3-(β-D-Glucopyranosyloxy)-5-methyl-4-[(4-propylphenyl)-methyl]-1*H*-pyrazole

[0067] The title compound was prepared in a similar manner to that described in Example 35 using 5-methyl-4-[(4-propylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl) methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-*D*-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
0.91 (3H, t, J=7.5Hz), 1.50-1.65 (2H, m), 2.05 (3H, s), 2.45-2.60 (2H, m), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.83 (1H, d, J=11.9Hz), 5.00-5.10 (1H, m), 7.00-7.15 (4H, m)

Example 37

3-(β-D-Glucopyranosyloxy)-4-[(4-isobutylphenyl)methyl]-5-methyl-1*H*-pyrazole

[0068] The title compound was prepared in a similar manner to that described in Example 35 using 4-[(4-isobutylphenyl)-methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm: 0.87 (6H, d, J=6.6Hz), 1.70-1.90 (1H, m), 2.04 (3H, s), 2.41 (2H, d, J=7.1Hz), 3.25-3.45 (4H, m), 3.55-3.90 (4H, m), 5.00-5.10 (1H, m), 6.95-7.15 (4H, m)

Example 38

3-(β-D-Glucopyranosyloxy)-5-methyl-4-[(4-propoxyphenyl)-methyl]-1*H*-pyrazole

[0069] The title compound was prepared in a similar manner to that described in Example 35 using 5-methyl-4-[(4-propoxyphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl) methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
1.02 (3H, t, J=7.4Hz), 1.65-1.80 (2H, m), 2.05 (3H, s), 3.25-3.45 (4H, m), 3.60-3.75 (3H, m), 3.80-3.90 (3H, m), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.05-7.15 (2H, m)

Example 39

4-[(4-Ethoxyphenyl)methyl]-3-(β-D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole

[0070] The title compound was prepared in a similar manner to that described in Example 35 using 4-[(4-ethoxyphenyl)-methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
1.34 (3H, t, J=7.0Hz), 2.05 (3H, s), 3.25-3.45 (4H, m), 3.60-3.75 (3H, m), 3.80-3.90 (1H, m), 3.97 (2H, q, J=7.0Hz), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.05-7.15 (2H, m)

Example 40

3-(β-D-Glucopyranosyloxy)-5-methyl-4-[(4-trifluoromethylphenyl)methyl]-1*H*-pyrazole

[0071] The title compound was prepared in a similar manner to that described in Example 35 using 5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-4-[(4-trifluoromethylphenyl)methyl]-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
2.08 (3H, s), 3.20-3.40 (4H, m), 3.67 (1H, dd, J=5.0, 11.9Hz), 3.75-3.90 (3H, m), 5.00-5.10 (1H, m), 7.30-7.45 (2H, m), 7.45-7.60 (2H, m)

Example 41

4-[(4-*tert*-Butylphenyl)methyl]-3-(β-D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole

[0072] The title compound was prepared in a similar manner to that described in Example 35 using 4-[(4-*tert*-butylphenyl)-methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
1.28 (9H, s), 2.06 (3H, s), 3.25-3.45 (4H, m), 3.60-3.90 (4H, m), 5.00-5.10 (1H, m), 7.05-7.15 (2H, m), 7.20-7.30 (2H, m)

Example 42

4-[(4-Butoxyphenyl)methyl]-3-(β-D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole

[0073] The title compound was prepared in a similar manner to that described in Example 35 using 4-[(4-butoxyphenyl)-methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
0.97 (3H, t, J=7.4Hz), 1.40-1.55 (2H, m), 1.65-1.80 (2H, m), 2.05 (3H, s), 3.30-3.45 (4H, m), 3.60-3.75 (3H, m), 3.83 (1H, d, J=12.0Hz), 3.91 (2H, t, J=6.4Hz), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.05-7.15 (2H, m)

Example 43

3-(β-D-Glucopyranosyloxy)-5-methyl-4-[(4-methylthiophenyl)methyl]-1*H*-pyrazole

[0074] The title compound was prepared in a similar manner to that described in Example 35 using 5-methyl-4-[(4-methylthiophenyl)methyl)-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl)-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
2.06 (3H, s), 2.42 (3H, s), 3.20-3.45 (4H, m), 3.55-3.75 (3H, m), 3.80-3.90 (1H, m), 5.00-5.10 (1H, m), 7.05-7.20 (4H, m)

Example 44

5-Ethyl-3-(β-D-glucopyranosyloxy)-4-[(4-methylthiophenyl)-methyl]-1*H*-pyrazole

[0075] The title compound was prepared in a similar manner to that described in Example 35 using 5-ethyl-4-[(4-meth-

ylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
1.06 (3H, t, J=7.6Hz), 2.42 (3H, s), 2.47 (2H, q, J=7.6Hz), 3.25-3.45 (4H, m), 3.60-3.80 (3H, m), 3.80-3.90 (1H, m), 5.00-5.10 (1H, m), 7.10-7.20 (4H, m)

Example 45

3-(β-D-Glucopyranosyloxy)-4-[(4-isopropylphenyl)methyl]-5-methyl-1*H*-pyrazole

[0076] The title compound was prepared in a similar manner to that described in Example 35 using 4-[(4-isopropylphenyl)-methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
1.20 (6H, d, J=6.9Hz), 2.05 (3H, s), 2.75-2.90 (1H, m), 3.25-3.45 (4H, m), 3.55-3.90 (4H, m), 5.00-5.10 (1H, m), 7.00-7.15 (4H, m)

Example 46

3-(β-D-Glucopyranosyloxy)-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-1*H*-pyrazole

[0077] The title compound was prepared in a similar manner to that described in Example 35 using 4-[(4-methylthiophenyl)-methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-gluco-pyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
2.42 (3H, s), 3.25-3.50 (4H, m), 3.69 (1H, dd, J=4.9, 12.0Hz), 3.75-3.90 (3H, m), 4.90-5.10 (1H, m), 7.10-7.20 (4H, m)

Example 47

4-Benzyl-3-(β-D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole

[0078] The title compound was prepared in a similar manner to that described in Example 35 using 4-benzyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl) methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
3.25-3.45 (4H, m), 3.67 (1H, dd, J=5.3, 12.0Hz), 3.80-3.95 (3H, m), 4.97 (1H, d, J=7.4Hz), 7.05-7.25 (5H, m)

Example 48

3-(β-D-Glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-5-trifluoromethyl-1*H*-pyrazole

[0079] The title compound was prepared in a similar manner to that described in Example 35 using 4-[(4-methoxyphenyl)-methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-gluco-pyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
3.25-3.45 (4H, m), 3.67 (1H, d, J=5.4, 12.1Hz), 3.73 (3H, s), 3.75-3.90 (3H, m), 4.90-5.00 (1H, m), 6.70-6.85 (2H, m), 7.05-7.15 (2H, m)

Example 49

3-(β-D-Glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-5-methyl-1*H*-pyrazole

[0080] The title compound was prepared in a similar manner to that described in Example 35 using 4-[(4-methoxyphenyl)-methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1H-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
2.04 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.73 (3H, s), 3.80-3.90 (1H, m), 5.00-5.10 (1H, m), 6.75-6.85 (2H, m), 7.05-7.15 (2H, m)

Example 50

4-Benzyl-3-(β-D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole

[0081] The title compound was prepared in a similar manner to that described in Example 35 using 4-benzyl-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
2.05 (3H, s), 3.25-3.45 (4H, m), 3.60-3.90 (4H, m), 5.00-5.10 (1H, m), 7.05-7.25 (5H, m)

Example 51

3-(β-D-Glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-1,5-dimethylpyrazole

[0082] The title compound was prepared in a similar manner to that described in Example 35 using 4-[(4-methoxyphenyl)-methyl]-1,5-dimethyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
2.06 (3H, s), 3.25-3.45 (4H, m), 3.55-3.70 (6H, m), 3.73 (3H, s), 3.75-3.90 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.05-7.15 (2H, m)

Example 52

3-(β-D-Glucopyranosyloxy)-1-methyl-4-[(4-methylthiophenyl)methyl]-5-trifluoromethylpyzole

[0083] The title compound was prepared in a similar manner to that described in Example 35 using 1-methyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethylpyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
2.42 (3H, s), 3.30-3.50 (4H, m), 3.69 (1H, dd, J=4.7, 12.0Hz), 3.75-3.90 (6H, m), 5.25-5.35 (1H, m), 7.05-7.20 (4H, m)

Example 53

1-Ethyl-3-(β-D-glucopyranosyloxy)-4-[(4-methylthiophenyl)-methyl]-5-trifluoromethylpyrazole

[0084] The title compound was prepared in a similar manner to that described in Example 35 using 1-ethyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethylpyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O* acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
1.38 (3H, t, J=7.1Hz). 2.42 (3H, s), 3.30-3.50 (4H, m), 3.60-3.75 (1H, m), 3.75-3.90 (1H, m), 4.14 (2H, q, J=7.1Hz), 5.25-5.35 (1H, m), 7.05-7.20 (4H, m)

Example 54

3-(β-D-Glucopyranosyloxy)-4-[(4-methylthiophenyl)methyl]-1-propyl-5-trifluoromethylpyrazole

[0085] The title compound was prepared in a similar manner to that described in Example 35 using 4-[(4-methylthiophenyl)-methyl]-1-propyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethylpyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
0.90 (3H, t, J=7.4Hz), 1.75-1.90 (2H, m), 2.42 (3H, s), 3.30-3.50 (4H, m), 3.69 (1H, dd, J=4.9, 12.0Hz), 3.75-3.90 (3H, m), 4.00-4.10 (2H, m), 5.25-5.35 (1H, m), 7.05-7.20 (4H, m)

Example 55

3-(β-D-Glucopyranosyloxy)-5-methyl-4-[(4-methylphenyl)-methyl]-1*H*-pyrazole

[0086] 5-Methyl-4-[(4-methylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole was

prepared in a similar manner to that described in Example 15 using 1,2-dihydro-5-methyl-4-[(4-methylphenyl)methyl]-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one. Then, the title compound was prepared in a similar manner to that described in Example 35 using 5-methyl-4-[(4-methylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
2.04 (3H, s), 2.26 (3H, s), 3.25-3.45 (4H, m), 3.55-3.90 (4H, m), 5.00-5.10 (1H, m), 6.95-7.15 (4H, m)

Example 56

4-[(4-Ethylphenyl)methyl]-3-(β-D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole

[0087] 4-[(4-Ethylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole was prepared in a similar manner to that described in Example 15 using 4-[(4-ethylphenyl)methyl]-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one. Then, the title compound was prepared in a similar manner to that described in Example 35 using 4-[(4-ethylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
1.18 (3H, t, J=7.6Hz), 2.04 (3H, s), 2.57 (2H, q, J=7.6Hz), 3.25-3.45 (4H, m), 3.55-3.90 (4H, m), 5.00-5.10 (1H, m), 6.95-7.20 (4H, m)

Example 57

3-(β-D-Glucopyranosyloxy)-4-[(4-methylphenyl)methyl]-5-trifluoromethyl-1*H*-pyrazole

[0088] 4-[(4-Methylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole was prepared in a similar manner to that described in Example 26 using 1,2-dihydro-4-[(4-methylphenyl)methyl]-5-trifluoromethyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-3*H*-pyrazol-3-one. Then, the title compound was prepared in a similar manner to that described in Example 35 using 4-[(4-methylphenyl)-methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl)-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
2.25 (3H, s), 3.20-3.45 (4H, m), 3.55-3.70 (1H, m), 3.70-3.90 (3H, m), 4.80-4.95 (1H, m), 6.90-7.15 (4H, m)

Example 58

4-[(4-Ethylphenyl)methyl]-3-(β-D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole

[0089] 4-[(4-Ethylphenyl)methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole was prepared in a similar manner to that described in Example 26 using 4-[(4-ethylphenyl)methyl]-1,2-dihydro-5-trifluoromethyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-3*H*-pyrazol-3-one. Then, the title compound was prepared in a similar manner to that described in Example 35 using 4-[(4-ethylphenyl)-methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
1.18 (3H, t, J=7.6Hz), 2.50-2.60 (2H, m), 3.15-3.40 (4H, m), 3.55-3.65 (1H, m), 3.70-3.90 (3H, m), 4.80-4.95 (1H, m), 6.95-7.15 (4H, m)

Example 59

3-(β-D-Glucopyranosyloxy)-4-[(4-isopropylphenyl)methyl]-5-trifluoromethyl-1*H*-pyrazole

[0090] 4-[(4-Isopropylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole was prepared in a similar manner to that described in Example 26 using 1,2-dihydro-4-[(4-isopropylphenyl)-methyl]-5-trifluoromethyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-methylthiophenyl)methyl]-5-trifluoro-methyl-3*H*-pyrazol-3-one. Then, the title compound was prepared in a similar manner to that described in Example 35 using 4-[(4-isopropylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole instead

of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
1.20 (6H, d, J=6.9Hz), 2.75-2.85 (1H, m), 3.15-3.40 (4H, m), 3.55-3.65 (1H, m), 3.70-3.90 (3H, m), 4.80-4.95 (1H, m), 7.00-7.15 (4H, m)

Example 60

4-[(4-Chlorophenyl)methyl]-3-(β-D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole

[0091] 4-[(4-Chlorophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole was prepared in a similar manner to that described in Example 26 using 4-[(4-chlorophenyl)methyl]-1,2-dihydro-5-trifluoromethyl-3H-pyrazol-3-one instead of 1,2-dihydro-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-3*H*-pyrazol-3-one. Then, the title compound was prepared in a similar manner to that described in Example 35 using 4-[(4-chlorophenyl)-methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
3.20-3.40 (4H, m), 3.55-3.70 (1H, m), 3.75-3.90 (3H, m), 4.80-4.95 (1H, m), 7.10-7.25 (4H, m)

Example 61

3-(β-D-Glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1-propylpyrazole

[0092] To a suspension of 3-(β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole (50mg) and cesium carbonate (0.20g) in *N,N*-dimethylformamide (1mL) was added iodopropane (0.036mL) at 50°C , and the mixture was stirred overnight. Water was added to the reaction mixture, and the resulting mixture was purified by solid phase extraction on ODS (washing solvent: distilled water, eluent: methanol). The resulting semi-purified material was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 8/1) to give 3-(β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1-propylpyrazole (28mg).
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
0.87 (3H, t, J=7.4Hz). 1.26 (6H, d, J=6.0Hz), 1.65-1.80 (2H, m), 2.07 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.75-3.95 (3H, m), 4.40-4.60 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

Example 62

1-Ethyl-3-(β-D-glucopyranosyloxy)-4-[(4-isopropylphenyl)-methyl]-5-methylpyrazole

[0093] The title compound was prepared in a similar manner to that described in Example 61 using iodoethane instead of iodopropane.
^{1}H-NMR (500MHz, CD_3OD) δ ppm: 1.26 (6H, d, J=6.0Hz), 1.29 (3H, t, J=7.2Hz), 2.08 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.75-3.90 (1H, m), 3.96 (2H, q, J=7.2Hz), 4.40-4.60 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

Example 63

1-Ethyl-3-(β-D-glucopyranosyloxy)-4-[(4-methoxyphenyl)-methyl]-5-methylpyrazole

[0094] The title compound was prepared in a similar manner to that described in Example 61 using 3-(β-D-glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-5-methyl-1*H*-pyrazole instead of 3-(β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole and using iodoethane instead of iodopropane.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
1.29 (3H, t, J=7.1Hz), 2.07 (3H, s), 3.20-3.45 (4H, m), 3.55-3.75 (6H, m), 3.82 (1H, dd, J=2.0, 12.0Hz), 3.90-4.05 (2H, m), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.05-7.15 (2H, m)

Example 64

3-(β-D-Glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-5-methyl-1-propylpyrazole

[0095] The title compound was prepared in a similar manner to that described in Example 61 using 3-(β-D-glucop-

yranosyloxy)-4-[(4-methoxyphenyl)methyl]-5-methyl-1*H*-pyrazole instead of 3-(β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
0.87 (3H, t, J=7.5Hz), 1.65-1.80 (2H, m), 2.07 (3H, s), 3.35-3.45 (4H, m), 3.60-3.75 (3H, m), 3.73 (3H, s), 3.75-3.85 (1H, m), 3.85-3.95 (2H, m), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.00-7.15 (2H, m)

Example 65

1-Ethyl-4-[(4-ethoxyphenyl)methyl]-3-(β-D-glucopyranosyloxy)-5-methylpyrazole

[0096] The title compound was prepared in a similar manner to that described in Example 61 using 4-[(4-ethoxyphenyl)-methyl]-5-methyl-3-(β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 3-(β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole and using iodoethane instead of iodopropane.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
1.28 (3H, t, J=7.4Hz), 1.34 (3H, t, J=7.2Hz), 2.07 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.75-3.85 (1H, m), 3.90-4.00 (4H, m), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.00-7.15 (2H, m)

Example 66

4-[(4-Ethoxyphenyl)methyl]-3-(β-D-glucopyranosyloxy)-5-methyl-1-propylpyrazole

[0097] The title compound was prepared in a similar manner to that described in Example 61 using 4-[(4-ethoxyphenyl)-methyl]-5-methyl-3-(β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 3-(β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
0.87 (3H, t, J=7.6Hz), 1.34 (3H, t, J=7.1Hz), 1.65-1.80 (2H, m), 2.07 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.81 (1H, dd, J=2.1, 12.1Hz), 3.85-4.05 (4H, m), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.00-7.15 (2H, m)

Example 67

1-Ethyl-4-[(4-ethylphenyl)methyl]-3-(β-D-glucopyranosyloxy)-5-methylpyrazole

[0098] The title compound was prepared in a similar manner to that described in Example 61 using 4-[(4-ethylphenyl)-methyl]-5-methyl-3-(β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 3-(β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole and using iodoethane instead of iodopropane.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
1.17 (3H, t, J=7.6Hz), 1.28 (3H, t, J=7.2Hz), 2.06 (3H, s), 2.56 (2H, q, J=7.6Hz), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.75-3.85 (1H, m), 3.90-4.00 (2H, m), 5.00-5.10 (1H, m), 7.00-7.15(4H, m)

Example 68

4-[(4-Ethylphenyl)methyl]-3-(β-D-glucopyranosyloxy)-5-methyl-1-propylpyrazole

[0099] The title compound was prepared in a similar manner to that described in Example 61 using 4-[(4-ethylphenyl)-methyl]-5-methyl-3-(β-D-glucopyranosyloxy)-1*H*-pyrazole instead of 3-(β-D-glucopyranosyloxy)-4-[(4-isopropoxyhenyl)methyl]-5-methyl-1*H*-pyrazole.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
0.87 (3H, t, J=7.4Hz), 1.17 (3H, t, J=7.6Hz), 1.65-1.80 (2H, m), 2.06 (3H, s), 2.56 (2H, q, J=7.6Hz), 3.25-3.45 (4H, m), 3.60-3.95 (6H, m), 5.00-5.10 (1H, m), 7.00-7.15 (4H, m)

Example 69

1-Butyl-3-(β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)-methyl]-5-methylpyrazole

[0100] The title compound was prepared in a similar manner to that described in Example 61 using bromobutane instead of iodopropane.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
0.92 (3H, t, J=7.4Hz), 1.20-1.40 (8H, m), 1.60-1.75 (2H, m), 2.07 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.81

(1H, dd, J=2.1, 12.0Hz), 3.91 (2H, t, J=7.2Hz), 4.45-4.55 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

Example 70

3-(β-D-Glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole

[0101] The title compound was prepared in a similar manner to that described in Example 61 using 2-bromopropane instead of iodopropane.
^{1}H-NMR (500MHz, CD_3OD) δ ppm:
1.26 (6H, d, J=6.0Hz), 1.30-1.40 (6H, m), 2.08 (3H, s), 3.15-3.45 (4H, m), 3.55-3.75 (3H, m), 3.78 (1H, dd, J=2.3, 12.0Hz), 4.35-4.45 (1H, m), 4.45- 4.55 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H,m)

Test Example 1

Assay for inhibitory effect on human SGLT2 activity

1) Construction of the plasmid vector expressing human SGLT2

[0102] Preparation of the cDNA library for PCR amplification was performed by reverse transcription of a total RNA derived from human kidney (Ori gene) with oligo dT as the primer, using Super Script preamplification system (Gibco-BRL: LIFE TECHNOLOGIES). The DNA fragment coding for human SGLT2 was amplified by the PCR reaction, in which the human kidney cDNA library described above was used as the template and the following oligo nucleotides 0702F and 0712R, presented as sequence number 1 and 2 respectively, were used as the primers. The amplified DNA fragment was ligated into pCR (Invitrogen), a vector for cloning, according to standard method of the kit. The *Escherichia coli* HB101 was transformed according to usual method and then selection of the transformants was performed on the LB agar medium containing 50 μg/mL of kanamycin. After plasmid DNA was extracted and purified from the one of the transformants, amplifying of the DNA fragment coding for human SGLT2 was performed by the PCR reaction, in which the following oligo nucleotides 0714F and 0715R, presented as sequence number 3 and 4 respectively, were used as the primers. The amplified DNA fragment was digested with restriction enzymes, Xho I and Hind III, and then purified with Wizard purification System (Promega). This purified DNA fragment was inserted at into the corresponding restriction sites of pcDNA3.1 (-) Myc/His-B (Invitrogen), a vector for expressing of fusion protein. The *Escherichia coli* HB101 was transformed according to the usual method and then selection of the transformant was performed on the LB agar medium containing 50 μg/mL of ampicillin. After plasmid DNA was extracted and purified from this transformant, the base sequence of the DNA fragment inserted at the multi-cloning sites of the vector pcDNA3.1 (-) Myc/His - B was analyzed. This clone had a single base substitution (ATC which codes for the isoleucine-433 was substituted by GTC) compared with the human SGLT2 reported by Wells *et al* (Am. J. Physiol., Vol. 263, pp. 459-465 (1992)). Sequentially, a clone in which valine is substituted for isoleucine-433 was obtained. This plasmid vector expressing human SGLT2 in which the peptide presented as sequence number 5 is fused to the carboxyl terminal alanine residue was designated KL29.

Sequence Number 1 ATGGAGGAGCACACAGAGGC

Sequence Number 2 GGCATAGAAGCCCCAGAGGA

Sequence Number 3 AACCTCGAGATGGAGGAGCACACAGAGGC

Sequence Number 4 AACAAGCTTGGCATAGAAGCCCCAGAGGA

Sequence Number 5 KLGPEQKLISEEDLNSAVDHHHHHH

2) Preparation of the cells expressing transiently human SGLT2

[0103] KL29, the plasmid expressing human SGLT2, was transfected into COS-7 cells (RIKEN CELL BANK RCB0539) by electroporation. Electroporation was performed with GENE PULSER II (Bio-Rad Laboratories) under the condition: 0.290 kV, 975 μF, 2 x 10^6 cells of COS-7 cell and 20 μg of KL29 in 500 μL of OPTI-MEM I medium (Gibco-BRL: LIFE TECHNOLOGIES) in the 0.4 cm type cuvette. After the gene transfer, the cells were harvested by centrifugation and resuspended with OPTI-MEM I medium (lmL/cuvette). To each well in 96-wells plate, 125 μL of this cell suspension was added. After overnight culture at 37 °C under 5 % CO_2, 125 μL of DMEM medium which is containing 10 % of fetal bovine serum (Sanko Jyunyaku), 100 units/mL sodium penicillin G (Gibco-BRL: LIFE TECHNOLOGIES), 100 μg/mL streptomycin sulfate (Gibco-BRL: LIFE TECHNOLOGIES) was added to each well. These cells were cultured until the next day and then they were used for the measurement of the inhibitory activity against the uptake of methyl-α-D-glucopyrenoside.

3) Measurement of the inhibitory activity against the uptake of methyl-α-D-glucopyranoside

[0104] After a test compounds was dissolved in dimethyl sulfoxide and diluted with the uptake buffer (a pH 7.4 buffer containing 140 mM sodium chloride, 2 mM potassium chloride, 1 mM calcium chloride, 1 mM magnesium chloride, 5 mM methyl-α-D-glucopyranoside, 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethane sulfonic acid and 5 mM tris(hydroxymethyl)aminomethane), each diluent was used as test sample for measurement of the inhibitory activity. After removal of the medium of the COS-7 cells expressing transiently human SGLT2, to each well 200 μL of the pretreatment buffer (a pH 7.4 buffer containing 140 mM choline chloride, 2 mM potassium chloride, 1 mM calcium chloride, 1 mM magnesium chloride, 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethane sulfonic acid and 5 mM tris(hydroxymethyl)aminomethane) was added, and the cells were incubated at 37 °C for 10 minutes. After the pretreatment buffer was removed, 200 μL of the same buffer was added again, and the cells were incubated at 37 °C for 10 minutes. The buffer for measurement was prepared by adding of 7 μL of methyl-α-D-(U-14C)glucopyranoside(Amersham Pharmacia Biotech) to 525 μL of the prepared test sample. For the control, the buffer for measurement without test compound was prepared. For estimate of the basal uptake in the absence of test compound and sodium, the buffer for measurement of the basal uptake, which contains 140 mM choline chloride in place of sodium chloride, was prepared similarly. After the pretreatment buffer was removed, 75 μL of the each buffer for measurement was added to each well, the cells were incubated at 37 °C for 2 hours. After the buffer for measurement was removed, 200 μL of the washing buffer (a pH 7.4 buffer containing 140 mM choline chloride, 2 mM potassium chloride, 1 mM calcium chloride, 1 mM magnesium chloride, 10 mM methyl-α-D-glucopyranoside, 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethane sulfonic acid and 5 mM tris(hydroxymethyl)aminomethane)was added to each well and immediately removed. After two additional washings, the cells were solubilized by addition of 75 μL of 0.2 N sodium hydroxide to each well. After the cell lysates were transferred to the PicoPlate (Packard) and 150 μL of MicroScint-40 (Packard) was added to each well, the radioactivity was measured with microplate scintillation counter TopCount (Packard). The difference in uptake was obtained as 100 % value by subtracting the radioactivity in the basal uptake from that in control and then the concentrations at which 50 % of uptake were inhibited (IC_{50}) were calculated from the concentration-inhibition curve by least square method. The results are shown in the following Table 1.

[Table 1]

Test compound	IC_{50} value (nM)
Example 35	181
Example 36	441
Example 37	346
Example 38	702
Example 39	185
Example 43	84
Example 44	509
Example 45	441
Example 46	679
Example 48	415

[Table 1] (continued)

Test compound	IC_{50} value (nM)
Example 49	383
Example 52	835
Example 55	280
Example 56	190
Example 58	634
WAY-123783	>100000

Test Example 2

Assay for the facilitatory effect on urinary glucose excretion

Method A)

[0105] As experimental animal, overnight fasted SD rats (SLC, male, 5 weeks of age, 120-150g) were used. Test compound (25.40 mg) was suspended in 762 μL of ethanol and dissolved by adding of 3.048 mL of polyethylene glycol 400 and 3.81 mL of saline and then 3.3 mg/mL solution was prepared. A part of this solution was diluted with the solvent (saline: polyethylene glycol 400: ethanol = 5: 4: 1) and then each solution at the concentration of 3.3, 1 or 0.33 (mg/mL) was prepared. Each of these solutions was subcutaneously administered to the rats at the dose of 3 mL/kg (10, 3 and 1 mg/kg). For the control, just the solvent (saline: polyethylene glycol 400: ethanol = 5: 4: 1) was subcutaneously administered at the dose of 3 mL/kg. Immediately after this subcutaneous administration, 200 g/L glucose solution was orally administered at the dose of 10 mL/kg (2 g/kg). The subcutaneous administration was performed with 26G needle and 1 mL syringe. The oral administration was performed with gastric tube for rat and 2.5 mL syringe. The head count in one group was 3. Collection of urine was performed in metabolic cage after these administrations were finished. The sampling time for collection of urine was 4 hours after the glucose administration. After collection of urine was finished, the urine volume was recorded and the urinary glucose concentration was measured. The glucose concentration was measured with a kit for laboratory test: Glucose B-Test WAKO (Wako Pure Chemical Industries, Ltd.). The amount of urinary glucose excretion in 4 hours per 1 body was calculated from urine volume and urinary glucose concentration.

Method B)

[0106] As experimental animal, overnight fasted SD rats (SLC, male, 7 weeks of age, 180-220g) were used. A test compound (10 mg) was suspended or dissolved in 300 μL of ethanol and dissolved by adding of 1.2 mL of polyethylene glycol 400 and 1.5 mL of saline and then 3.3 mg/mL solution was prepared. A part of this solution was diluted with the solvent (saline: polyethylene glycol 400: ethanol = 5: 4: 1) and then each solution at the concentration of 3.3, 0.33 or 0.033 (mg/mL) was prepared. After the body weights of the rats were measured, the test compound solution was administered by intravenous injection to the tail vein at the dose of 3 mL/kg (10, 1 and 0.1 mg/kg). For the control, just the solvent (saline: polyethylene glycol 400: ethanol = 5: 4: 1) was administered by intravenous injection to the tail vein at the dose of 3 mL/kg. Immediately after this intravenous administration, 200 g/L glucose solution was orally administered at the dose of 10 mL/kg (2 g/kg). The intravenous administration was performed with 26G needle and 1 mL syringe. The oral administration was performed with gastric tube for rat and 2.5 mL syringe. The head count in one group was 3. Collection of urine was performed in metabolic cage after the glucose administration was finished. The sampling time for collection of urine was 24 hours after the glucose administration. After collection of urine was finished, the urine volume was recorded and the urinary glucose concentration was measured. The glucose concentration was measured with a kit for laboratory test: Glucose B-Test WAKO (Wako Pure Chemical Industries, Ltd.). The amount of urinary glucose excretion in 24 hours per 200 g of body weight was calculated from urine volume, urinary glucose concentration and body weight.
The results are shown in the following Table 2.

[Table 2]

Test compound	Method	Dose (mg/kg)	Amount of Urinary Glucose Excretion (mg)
Example 35	B	0.1	16
		1	74
		10	188
Example 45	A	1	22.1
		3	83.2
		10	153.3
	B	0.1	2
		1	45
		10	132

Test Example 3

Acute toxicity test

Method A)

[0107] By adding 0.5% sodium carboxymethylcellulose solution to the test compound, 100 mg/mL suspension was prepared. As experimental animal, male 6-7 weeks of age ICR mice fasted for 4 hours (Clea Japan, 28-33g, 5 animals in each group) were used. The test suspension described above was orally administered to the experimental animals described above at the dose of 10 mL/kg (1000 mg/kg) and then observation was performed until 24 hours after the administration.

Method B)

[0108] By adding of the solvent (saline: polyethylene glycol 400: ethanol = 5 : 4: 1) to the test compound, 200 mg/mL suspension was prepared. As experimental animal, male 5 weeks of age ICR mice fasted for 4 hours (Clea Japan, 26-33g, 5 animals in each group) were used. The test suspension described above was subcutaneously administered to the experimental animals described above at the dose of 3 mL/kg (600 mg/kg) and then observation was performed until 24 hours after the administration.

[0109] The results are shown in the following Table 3.

[Table 3]

Test compound	Method	Death number
Example 35	B	0 / 5
Example 45	A	0 / 5

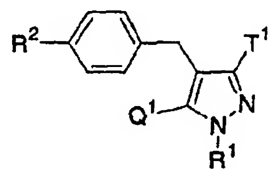
Industrial Applicability

[0110] The glucopyranosyloxybenzylbenzene derivatives represented by the above general formula (I) of the present invention and pharmaceutically acceptable salts thereof have an inhibitory activity on human SGLT2 and exert an excellent hypoglycemic effect by excreting excess glucose in the urine through preventing the reabsorption of glucose at the kidney. Therefore, agents for the prevention or treatment of diabetes, diabetic complications, obesity or the like can be provided comprising the glucopyranosyloxybenzylbenzene derivative represented by the above general formula (I) of the present invention or pharmaceutically acceptable salt thereof.

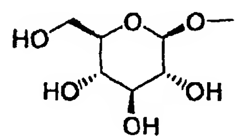
[0111] In addition, the compounds represented by the above general formulae (V) and (VII), and salts thereof are important as intermediates in the production of the compounds represented by the above general formula (I) and pharmaceutically acceptable salts thereof. Accordingly, the compounds represented by the above general formula (I) of the present invention and pharmaceutically acceptable salts thereof can be readily prepared via these compounds.

Claims

1. A glucopyranosyloxypyrazole derivative represented by the general formula:

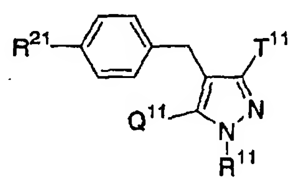


wherein R^1 represents a hydrogen atom or a lower alkyl group; one of Q^1 and T^1 represents a group represented by the formula:

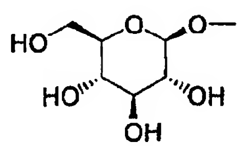


while the other represents a lower alkyl group or a halo(lower alkyl) group; R^2 represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom, or a pharmaceutically acceptable salt thereof.

2. A glucopyranosyloxypyrazole derivative as claimed in claim 1, represented by the general formula:

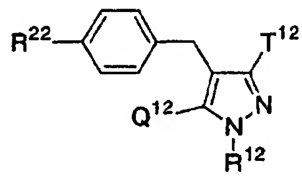


wherein R^{11} represents a hydrogen atom or a straight-chained or branched alkyl group having 1 to 3 carbon atoms; one of Q^{11} and T^{11} represents a group represented by the formula:

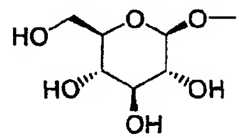


while the other represents a straight-chained or branched alkyl group having 1 to 3 carbon atoms; and R^{21} represents a straight-chained or branched alkyl group having 1 to 4 carbon atoms, a straight-chained or branched alkoxy group having 1 to 3 carbon atoms or a straight-chained or branched alkylthio group having 1 to 3 carbon atoms, or a pharmaceutically acceptable salt thereof.

3. A glucopyranosyloxypyrazole derivative as claimed in claim 1, represented by the general formula:



wherein R^{12} represents a hydrogen atom, an ethyl group, a propyl group or an isopropyl group; one of Q^{12} and T^{12} represents a group represented by the formula:



while the other represents a methyl group; and R^{22} represents an ethyl group, an ethoxy group, an isopropoxy group or a methylthio group, or a pharmaceutically acceptable salt thereof.

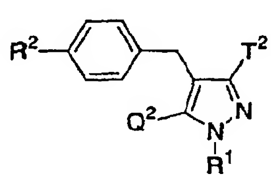
4. A pharmaceutical composition comprising as an active ingredient a glucopyranosyloxypyrazole derivative as claimed in claim 1, 2 or 3, or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition as claimed in claim 4 wherein the composition is a human SGLT2 inhibitor.

6. A pharmaceutical composition as claimed in claim 4 wherein the composition is an agent for the prevention or treatment of diabetes.

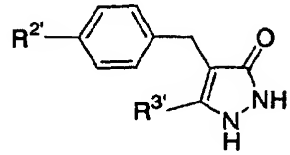
7. A pharmaceutical composition as claimed in claim 4 wherein the composition is an agent for the prevention or treatment of obesity.

8. A glucopyranosyloxypyrazole derivative represented by the general formula:



wherein R^1 represents a hydrogen atom or a lower alkyl group; one of Q^2 and T^2 represents a 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy group, while the other represents a lower alkyl group or a halo(lower alkyl) group; and R^2 represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo (lower alkyl) group or a halogen atom, or a salt thereof.

9. A benzylpyrazole derivative represented by the general formula:



wherein $R^{2'}$ represents a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom; and $R^{3'}$ represents a lower alkyl group, or a salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/05678

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07H17/02, C07D231/20, A61K31/7056, A61P3/04, 3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07H17/02, C07D231/20, A61K31/7056, A61P3/04, 3/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS(STN), MEDLINE(STN), EMBASE(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, 524111, A (Department of Medicinal Chemistry and Analytical Chemistry), 28 December, 1993 (28.12.93) & US, 5264451, A	1-9
A	US, 5264451, A (American Home Products Corp.), 23 November, 1993 (23.11.93) & US, 5274111, A	1-9
A	KUEBAL B., 'Simple synthesis of 4-(heteroarylmethyl) phenols and their acylation.' Liebigs Ann. Chem., 1980, Vol.9, pages 1392 to 1401 & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN.94 : 47172	9
A	PEERCE B.E., 'Molecular mechanism of two noncompetitive inhibitors of sodium-glucose cotransporter : comparison of DCCD and PCMB.', Am. J. Physiol., 1993, Vol.264, No.2, Pt.1, pages G300 to G305 & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIBTY (ACS), (Columbus, OH, USA), DN.118 : 228571	5-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search 06 November, 2000 (06.11.00)	Date of mailing of the international search report 14 November, 2000 (14.11.00)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

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